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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/215,163	12/18/1998	JEFFREY R. STINSON	50111/043002	7721

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER

ZEMAN, ROBERT A

ART UNIT	PAPER NUMBER
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1645

NOTIFICATION DATE	DELIVERY MODE
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06/29/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	09/215,163	STINSON ET AL.	
	Examiner	Art Unit	
	ROBERT A. ZEMAN	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44,54,55,57 and 61-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44,54,55,57 and 61-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>8-15-2008 and 3-13-2009</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-13-2009 has been entered.

Information Disclosure Statement

The Information Disclosure Statements filed on 8-15-2008 and 3-13-2009 have been considered. Initialed copies are attached hereto.

The amendment and response filed on 4-15-2009 are acknowledged. Claims 44, 54-55, 57 and 61-63 have been amended. 1, 17-19, 23, 29, 34-38, 47, 56 and 58-60 have been canceled. Claim 64 has been added. Claims 44, 54-55, 57 and 61-64 are pending and currently under examination.

Claim Objections Withdrawn

The objection to claim 1 for referring to Figures 3 and 6 is withdrawn. Cancellation of said claim has rendered the objection moot.

Claim Rejections Withdrawn

The rejection of claims 19, 47, 56 and 61 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase “said variable region consists of the murine “X” (ATCC Accession No. X) variable region” is withdrawn. Cancellation of said claims has rendered the rejection moot.

The rejection of claims 1, 17-19, 23, 29, 34-38, and 56-60 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272 in view of Carter et al. (WO 94/04679) is withdrawn. Cancellation of said claims and the amendment to claim 56 has rendered the rejection moot.

The provisional rejection of claims 1, 17-18, 23, 37 and 56-60 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-36 and 38 of copending Application No. 11/788,546 is withdrawn. Cancellation of said claims and the amendment to claim 56 has rendered the rejection moot.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 44, 54-55, 57 and 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Carter et al. (WO 94/04679) and Tzipori et al. (U.S.2003/0082189 A1 – IDS) for the reasons set forth in the previous Office action in the rejection of claims 1, 17-19, 23, 29, 34-38, 44, 47 and 54-63.

Applicant argues:

1. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to humanize their antibodies and then combine both antibodies in a pharmaceutical composition.
2. Carter describes general methods of humanizing an antibody and fails to describe or even mention either the 13C4 or 11E10 antibody.
3. Tzipori fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes different antibodies and fails to even mention 13C4 and 11E10.

4. The 13C4 and 11E10 antibodies were known at the time Tzipori et al. was filed. Given that Tzipori et al. did not utilize them in his studies demonstrates that the skilled artisan would not choose to humanize 13C2 or 11E10, humanize them, and combine the antibodies in a pharmaceutical composition.

5. As exhibited by Exhibit B, there is an unmet medical need for treating infections resulting from Shiga toxin producing bacteria and that Applicant's antibodies address this unmet need.

Applicant's arguments have been fully considered and deemed non-persuasive

With regard to Point 1, Applicant is reminded that the rejected claims are product claims and as such any intended use does not constitute a claim limitation. As the antibodies resulting from the combination of the cited references are the same as those of the instant invention, they would necessarily have the same binding affinities and immunological properties. Therefore, all the limitations of the instant claims are met. Finally, contrary to Applicant's assertion, Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Points 2 and 3, in the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, Tzipori et al. disclose that the anti-Shiga toxin antibodies are either human monoclonal antibodies or chimeric monoclonal antibodies (see paragraph [0004]).

With regard to Point 4, contrary to Applicant's assertion, the skilled artisan would, upon reading all the cited references, would elect to humanize the 13C4 and 11E10 antibodies. In the

Art Unit: 1645

instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, in view of the KSR decision, since the process of humanization of murine antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]). Moreover, MPEP 2144.06 states:

“It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to Point 5, as Tzipori et al. disclosed a method for treating Shiga-toxin related diseases (i.e. HUS) prior to the instant invention, the criteria set forth in MPEP 716.04 has not been met. Consequently, the rejection is deemed proper and is maintained.

As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies.

They differ from the instant invention in that they don't disclose humanized forms of said antibodies.

Carter et al. disclose the methods of producing humanized antibodies.

Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome (see abstract).

Consequently, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Carter et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of

Art Unit: 1645

humanizing a known antibody is well known in the art. One would have been motivated to humanize said antibodies in order to use them in the treatment methodologies disclosed by Tzipori et al. Moreover, since the humanization of antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody including the antibodies of Speirs or O'Brien (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]). Moreover, MPEP 2144.06 states:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

One would have had a reasonable expectation of success, as humanizing antibodies is a well-established method within the art. Furthermore, though the sequences of said antibodies where not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods.

Claims 44, 54-55, 57 and 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spiers et al. (Canadian Journal of Microbiology, 1991, Vol. 37, pages 650-653) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692) and Tzipori et al. (U.S.2003/0082189 A1 – IDS) for the reasons set forth in the previous Office action in the rejection of claims 1, 17-19, 23, 29, 34-34, 44, 47 and 54-63.

Applicant argues:

1. There is nothing in Speirs or O'Brien that teaches, suggests, or motivates the skilled worker to humanize their antibodies and then combine both antibodies in a pharmaceutical composition.

Art Unit: 1645

2. Shitara et al. describe general methods of humanizing an antibody and fails to describe or even mention either the 13C4 or 11E10 antibody.
3. Tzipori fails to provide motivation to produce the claimed humanized 13C4 and 11E10 antibodies because Tzipori describes different antibodies and fails to even mention 13C4 and 11E10.
4. The 13C4 and 11E10 antibodies were known at the time Tzipori et al. was filed. Given that Tzipori et al. did not utilize them in his studies demonstrates that the skilled artisan would not choose to humanize 13C2 or 11E10, humanize them, and combine the antibodies in a pharmaceutical composition.
5. As exhibited by Exhibit B, there is an unmet medical need for treating infections resulting from Shiga toxin producing bacteria and that Applicant's antibodies address this unmet need.

Applicant's arguments have been fully considered and deemed non-persuasive

With regard to Point 1, Applicant is reminded that the rejected claims are product claims and as such any intended use does not constitute a claim limitation. As the antibodies resulting from the combination of the cited references are the same as those of the instant invention, they would necessarily have the same binding affinities and immunological properties. Therefore, all the limitations of the instant claims are met. Finally, contrary to Applicant's assertion, Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome.

With regard to Points 2 and 3, in the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like

Art Unit: 1645

13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, Tzipori et al. disclose that the anti-Shiga toxin antibodies are either human monoclonal antibodies or chimeric monoclonal antibodies (see paragraph [0004]).

With regard to Point 4, contrary to Applicant's assertion, the skilled artisan would, upon reading all the cited references, would elect to humanize the 13C4 and 11E10 antibodies. In the instant rejection the motivation to humanize is provided by Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome. Moreover, in view of the KSR decision, since the process of humanization of murine antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]). Moreover, MPEP 2144.06 states:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to Point 5, as Tzipori et al. disclosed a method for treating Shiga-toxin related diseases (i.e. HUS) prior to the instant invention, the criteria set forth in MPEP 716.04 has not been met. Consequently, the rejection is deemed proper and is maintained

As outlined previously, Spiers et al. and O'Brien disclose the 11E10 and 13C4 antibodies.

They differ from the instant invention in that they don't disclose humanized forms of said antibodies.

Shitara et al. disclose the methods of producing humanized antibodies.

Tzipori et al. disclose that monoclonal antibodies specific for Shiga toxins (i.e. like 13C4 and 11E10) can be used to treat hemolytic uremic syndrome (see abstract).

Consequently, it would have been equally obvious for one of skill in the art to employ the methodologies disclosed by Shitara et al. to humanize the 13C4 and 11E110 antibodies in order to reduce the side effects associated with anti-mouse immunoglobulins since the process of humanizing a known antibody is well known in the art. One would have been motivated to humanize said antibodies in order to use them in the treatment methodologies disclosed by Tzipori et al. Moreover, since the humanization of antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody including the antibodies of Speirs or O'Brien (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]). Moreover, MPEP 2144.06 states:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

One would have had a reasonable expectation of success, as humanizing antibodies is a well-established method within the art. Furthermore, though the sequences of said antibodies were not explicitly disclosed it would have been standard practice for one of skill in the art to obtain said sequences utilizing standard sequencing methods.

New Grounds of Rejection

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

Art Unit: 1645

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 44, 54-55, 57 and 61-64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,747,272.

Although the conflicting claims are not identical, they are not patentably distinct from each other because

Patent 5,747,272 discloses the murine antibodies 11E10 and 13C4 in claim 9. Carter et al. disclose methods of humanizing murine antibodies and in order to reduce the side effects associated with anti-mouse immunoglobulins. Consequently, it would have been obvious for the skilled artisan to humanize the antibodies of patent 5,747,272 to minimize the side effects of murine antibodies. Moreover, since the humanization of antibodies is well known in the art yielding predictable results, it is obvious for the skilled artisan to humanize any murine antibody including the antibodies of the '272 patent (see *KSR International Co. v. Teleflex Inc.*, No. 04-1350 [U.S. Apr. 30, 2007]).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 44, 54-55 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is rendered vague and indefinite by the use of the phrase “comprises a variable region consisting of the immunoglobulin heavy chain and light chain variable regions as set forth in SEQ ID NO:19 and 21.” It is unclear which sequence correlates to a given variable region. Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert A. Zeman/
Primary Examiner, Art Unit 1645
June 18, 2009